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THE RENAL EFFECTS OF LOW-DOSE DOPAMINE IN THERMALLY INJURED PATIENTS

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The renal effects of low-dose dopamine (LDD) therapy in hyperdynamic thermally injured patients are unknown. We investigated the renal effects of LDD in ten burn patients (mean ± SEM age and %total body surface burned: 30.2 ± 3.3 years and 53.4% ± 7%) and six controls (mean age; 20.2 ± 0.5 years). Administration of LDD significantly increased glomerular filtration rate, effective renal plasma flow, sodium excretion, and urine flow in the controls and effective renal plasma flow, urine flow, heart rate, and cardiac index in the patients. The chronotropic effect of dopamine appears to be a principal contributor to the patients' increased effective renal plasma flow. Sodium excretion was increased by LDD only in the patients in whom the pre-dopamine sodium excretion exceeded 5 mEq/h. Lack of a consistent natriuretic effect and the consistent chronotropic effect suggest that the routine use of low-dose dopamine in burn patients is unwarranted. The side effects that attend the desired response determine clinical use, i.e., the potential for blood flow redistribution and increased cardiac work demands must be balanced against increased renal plasma flow and natriuresis.

INTRAVENOUS DOPAMINE is frequently administered to critically ill patients, with its wide use based upon the range of effects, which are infusion rate dependent. The dose-related pharmacologic actions result from selective stimulation of alpha-, beta-, and dopamine-adrenergic receptors. In normal humans, infusion rates less than 1 μg/kg/min primarily stimulate dopamine-1 and dopamine-2 receptors, resulting in vasodilatation and increased blood flow to renal, mesenteric, cerebral, and coronary vascular beds. As the dosage is increased, additional stimulation of beta-adrenergic receptors produces direct positive inotropic and chronotropic effects with a concomitant increase in cardiac output. When infusion rates exceed 10 μg/kg/min, alpha-1 and alpha-2 receptor stimulation is affected and systemic vascular resistance increases.

Renal blood flow alterations are a consequence of direct renal vascular dopamine receptor stimulation as well as systemic changes in blood pressure and cardiac output. The natriuretic effect of dopamine has been demonstrated in the absence of alterations in renal blood flow and is primarily mediated by inhibition of proximal renal tubular sodium transport.[1] The end result of these effects is an increase in urine output and sodium excretion.[2-5]

These renal-specific dopamine effects have encouraged intensivists to extrapolate the results from normal subjects to critically ill patients. The finding of altered receptor sensitivity to low-dose dopamine in some patient populations questions the validity of this assumption,[6] and few data exist that can support wide-scale use of low-dose dopamine. The objective of this study was to evaluate the effect of low-dose dopamine therapy in thermally injured patients by documenting its effect on effective renal plasma flow, glomerular filtration rate, sodium excretion, free water clearance, and cardiac function. This study focused on severely burned patients since we have previously reported a significant decrement in blood volume with concomitant changes in hormonal control mechanisms despite a hyperdynamic circulation.[7]

METHOD AND MATERIALS

Subjects

This protocol was approved by the authors' local institutional review board and the U.S. Army Surgeon General's Human Use Review Board. Informed consent was obtained from all participants before the study.

Six adult control subjects without a history of pre-existing cardiac or renal disease were admitted 1 day before study. Twelve hours before study, intravenous dextrose in half-normal saline was administered at an infusion rate sufficient to achieve a urine flow rate of approximately 2 mL/min.

Ten thermally injured patients with burns exceeding 30% of the total body surface area were enrolled in the study. All

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patients underwent uneventful resuscitation and were studied between the second and fourth postburn weeks. At the time of enrollment, all patients were without signs of infection or sepsis. Patients with pre-existing renal or cardiac disease were excluded from the study. Patients were not studied within 48 hours of a surgical procedure. On the night before study, the patients' intravenous fluid administration rates were altered to produce a urine flow rate of 2 mL/min. Composition of the intravenous fluids was tailored according to each patient's fluid and electrolyte status. A Swan-Ganz catheter was placed in all patients but not the controls for measurement of cardiac output and pulmonary artery occlusion pressures. Routine morning burn care was postponed on the day of study until completion of the protocol.

Study Procedure

On the morning of study, patients and control subjects were observed for 3 hours to ensure hemodynamic stability and a constant urine flow rate. Enteral feedings were continued at a constant infusion rate in the patients. Isotopic tracers for assessment of renal function were then infused. Urine produced during each hour of the study was collected for electrolyte and osmolality determinations, and multiple plasma samples were collected at precisely timed intervals for analysis of serum electrolytes, osmolality, and isotope concentration. Beginning 3 hours after initiation of the isotope infusion, dopamine was administered at a rate of 3 μg/kg/min by continuous intravenous infusion into a central vein. After 3 hours, the dopamine infusion was discontinued, and the isotope infusion and data collection continued for 1 additional hour.

Data collected in the control group consisted of heart rate, blood pressure, core temperature, hourly determinations of serum and urine Na^+, osmolality, urea, and creatinine, as well as a record of all fluids received and urine output. Additionally, in the patients, pulmonary artery pressure, pulmonary artery occlusion pressure, central venous pressure, and cardiac output were measured. From these data, stroke volume, systemic vascular resistance, and mean arterial pressure were calculated. The mean ± SEM of each variable was then calculated from all collected data for the time period before dopamine infusion and the period during dopamine infusion. Continuous cardiac monitoring and pulse oximetry were performed on all research subjects.

Sodium was measured by flame photometry and osmolality by vapor pressure. Infusions of ^{99m}Tc-diethylene-triamine penta-acetic acid (TcDTPA), 3.3 mCi in 150 mL 5% dextrose (10 mL/h), and ^{131}I-hippuran (IHIP), 0.36 mCi in 150 mL (15 mL/h) were begun just before TcDTPA (22 mL) and IHIP (15 mL) were given as a priming bolus (t = 0). Heparinized plasma (for counting of gamma activity in the spectral window for each isotope usually to less than 1% coefficient of variation) was sampled at 15-minute intervals between t = 1 hour and t = 2 hours, and at 30-minute intervals thereafter. The activity in a separate dilution of each infusate allowed determination of the rate of isotope infusion as well as the proportion of spillover of ^{131}I cpm into the ^{99m}Tc channel. All specimen counts were corrected for background (<1% for ^{99m}Tc and <5% for ^{131}I), ^{131}I spillover (approximately 23% of ^{131}I cpm), and decay time in the counting sequence. Plasma gamma activity for both isotopes was usually stable after t = 1 hour. After stability was reached, TcDTPA clearance (glomerular filtration rate, GFR) and IHIP clearance (effective renal plasma flow, RPF) were calculated (mL/min) each hour as the infusion rate (cpm/min) divided by the respective plasma activity (cpm/mL).[8,9]

Statistical Analysis

Pre-dopamine infusion data were compared between the control and patient populations utilizing a two-tailed *t* test and nonparametric analysis (Wilcoxon Rank Sum test) when variances differed. The effect of dopamine therapy within each population was analyzed using a paired *t* test. Comparison of variables was by correlation analysis. All analyses were performed using BMDP Software (Los Angeles, Calif).

RESULTS

Ten patients and six normal control subjects were enrolled in this study. Table 1 contains demographic data for both groups.

Pre-dopamine Data

Table 2 contains pre-dopamine hemodynamic and fluid administration data for both groups. Patients had significantly higher heart rates and mean arterial pressures, a reflection of the anticipated hemodynamic response to injury typical of thermally injured patients. Urine flow was significantly less in the patients, despite a significantly greater fluid administration rate. This is considered to reflect both the increased circulating levels of antidiuretic hormone we have previously reported in thermally injured patients[7] and an elevated evaporative water loss. Table 3 contains further hemodynamic data confirming the presence of a hyperdynamic response in the patients.

Table 4 contains pre-infusion renal function data for both groups. As expected, patients had significantly higher GFR and RPF, and lower free water clearance and fractional excretion of sodium than controls.

Table 1
Demographics

	Controls	Patients
Age (years)	20.2* ± 0.5 (19–22)	30.2 ± 3.3 (19–53)
Sex (M:F)	6:0	8:2
PBD†	—	19.5 ± 2.5 (9–32)
TBSAB‡ (%)	—	53.4 ± 7.0 (30–91)
Number	6	10

* Mean ± SEM.
† PBD = Postburn day of study.
‡ TBSAB = Total body surface area burn.

Table 2
Comparison of pre-dopamine hemodynamics and fluid status

	MAP*	HR†	Urine Flow‡	Fluid Infusion Rate (mL/h)
Controls	74 ± 2.8	61.4 ± 1.8	204 ± 30	239 ± 5
Patients	82.5 ± 2.6§	125 ± 2.7§	111 ± 22§	388 ± 26§

* Mean Arterial Pressure (mm Hg).
† Heart rate (beats/min).
‡ Urine flow (mL/h/1.73 m^2).
§ $p < 0.05$ compared with controls.

Table 3
Hemodynamic effects of dopamine in patients

	Pre-dopamine	Dopamine
Heart rate (beats/min)	125 ± 2.7	131 ± 2.9*
Mean Arterial Pressure (mm Hg)	82.5 ± 2.6	77.4 ± 2.6*
Stroke volume (mL)	119 ± 4	122 ± 4
Systemic vascular resistance (dynes/sec·cm²)	205 ± 11	183 ± 10.3*
Cardiac index (L/min·m²)	7.6 ± 0.30	8.03 ± 0.34*
Pulmonary Artery Occlusion Pressure (mm Hg)	9.4 ± 1.2	9.0 ± 0.8

* $p < 0.05$ compared with pre-dopamine.

Table 4
Pre-dopamine renal function

	Controls	Patients
Glomerular filtration rate (mL/min·1.73 m²)	118 ± 45	151 ± 7.0*
Renal plasma flow (mL/min·1.73 m²)	511 ± 25	678 ± 54*
Osmolar clearance (mL/min·1.73 m²)	2.91 ± 0.04	3.23 ± 0.4
Free water clearance (mL/min·1.73 m²)	0.48 ± 0.21	−1.38 ± 0.34*
Fractional excretion of sodium (%)	1.2 ± 0.2	0.70 ± 0.3*

* $p < 0.05$ compared with controls.

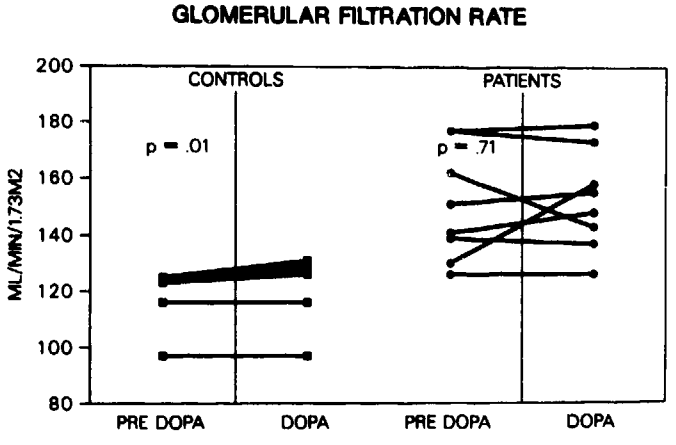

Figure 1. Glomerular filtration rate: the GFR for each control and patient is depicted before and during dopamine therapy. The GFR was consistently increased by dopamine in the controls (n = 6), but not the patients (n = 8).

Effect of Dopamine

Renal dose dopamine (3 μg/kg/min) significantly increased GFR, RPF, urine flow, osmolar clearance, sodium excretion, and fractional excretion of sodium (FENA) in the controls, whereas mean arterial pressure, heart rate, and free water clearance were unchanged (Figs. 1–4; Table 5). In the patients, renal dose dopamine significantly increased RPF, urine flow, free water clearance, FENA, Cardiac Index, and heart rate while decreasing mean arterial pressure and systemic vascular resistance (Figs. 1–5; Tables 3 and 6). In the patients, there

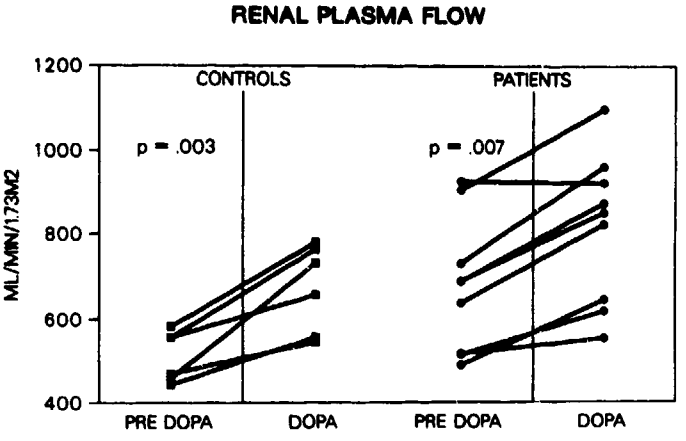

Figure 2. Renal plasma flow: This figure depicts renal plasma flow for each control (n = 6) and patient (n = 9) before and during dopamine therapy. Low-dose dopamine significantly increased renal plasma flow in both populations.

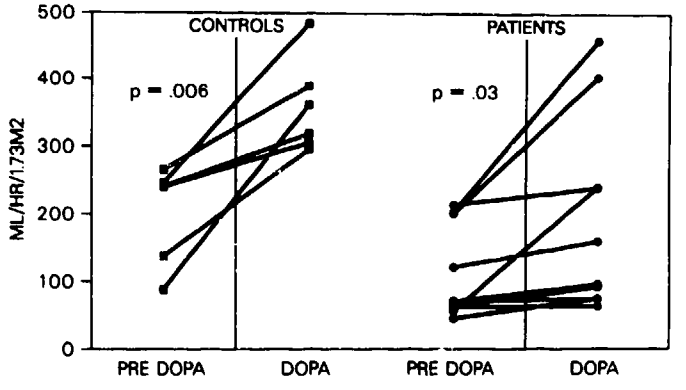

Figure 3. Urine output: This figure depicts urine flow for each control (n = 6) and patient (n = 10) before and during dopamine therapy. Low-dose dopamine significantly increased urine flow in both populations, although the effect was more pronounced in the controls.

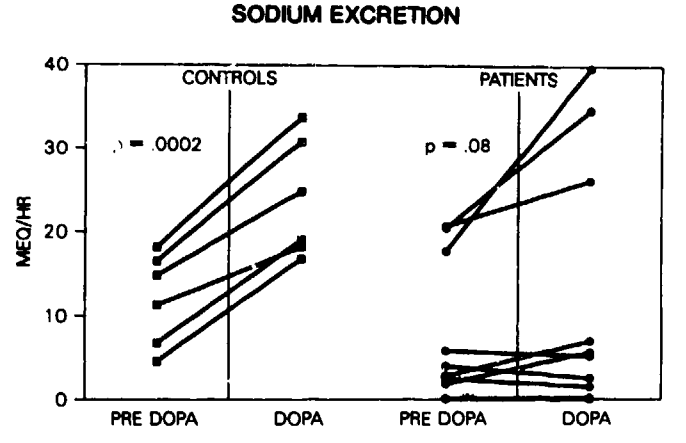

Figure 4. Sodium excretion: This figure depicts sodium excretion in milliequivalents per hour for each control (n = 6) and patient (n = 10) before and during dopamine therapy. All control subjects demonstrated a marked increase in sodium excretion with dopamine. The effect was inconsistent in the patients, with the majority showing none or a relatively small increase in sodium excretion with dopamine.

Table 5
Effects of dopamine in controls

	Pre-dopamine	Dopamine
Glomerular filtration rate (mL/min/1.73 m²)	118 ± 4.5	122 ± 5.3*
Effective renal plasma flow (mL/min/1.73 m²)	511 ± 25	673 ± 42*
Urine flow (mL/h/1.73 m²)	204 ± 30	360 ± 29*
Osmolar clearance (mL/min/1.73 m²)	2.9 ± 0.4	5.2 ± 0.6*
Fractional excretion of sodium (%)	1.25 ± 0.2	2.4 ± 0.2*
Sodium excretion (mEq/h)	12.0 ± 2.3	23.9 ± 2.9*
Mean Arterial Pressure (mm Hg)	74 ± 2.4	71 ± 2.9
Heart rate (beats/min)	61.5 ± 1.8	65 ± 2.9

*$p < 0.05$ compared with pre-dopamine.

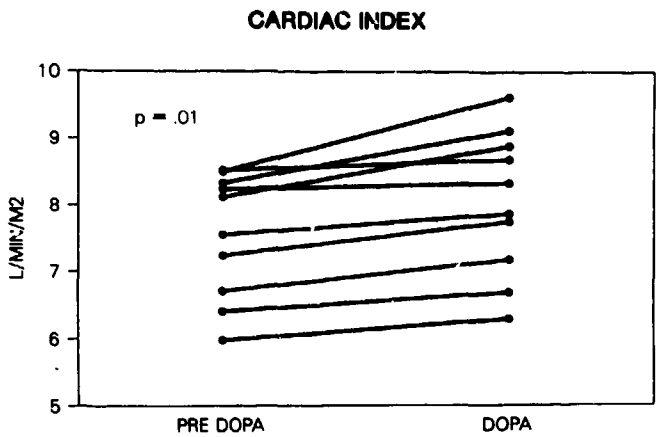

Figure 5. Cardiac Index: Cardiac Index for each patient (n = 10) is depicted before and during dopamine therapy. Low-dose dopamine significantly increased cardiac index in each patient.

Table 6
Effects of dopamine in patients (renal function)

	Pre-dopamine	Dopamine
Glomerular filtration rate (mL/min/1.73 m²)	151 ± 7.0	152 ± 5.3
Effective renal plasma flow (mL/min/1.73 m²)	678 ± 54	816 ± 59*
Urine flow (mL/h/1.73 m²)	111 ± 22	190 ± 45*
Osmolar clearance (mL/min/1.73 m²)	3.2 ± 0.4	3.96 ± 0.6
Sodium excretion (mEq/h)	7.6 ± 2.7	12.2 ± 4.8
Fractional excretion of sodium (%)	0.7 ± 0.2	1.1 ± 0.4*
Free water clearance (mL/min/1.73 m²)	−1.38 ± 0.33	−0.786 ± 0.35*

*$p < 0.05$ compared with pre-dopamine.

was no univariate correlation between burn size and changes in RPF, GFR, urine flow, sodium excretion, or cardiac function. Changes in urine output did not reflect changes in GFR in either population. However, changes in urine output did accurately predict changes in sodium excretion in the patients ($r = 0.811$; $p = 0.004$). Finally, natriuresis did not correlate with changes in renal blood flow.

DISCUSSION

The use of low doses of dopamine to maintain renal perfusion in critically ill patients is common, despite the relative lack of data to support its use. We have demonstrated that dopamine infused at a rate of 3 μg/kg/min increases renal blood flow in post-resuscitative thermally injured patients, although the mechanism does not appear to be solely dependent on dopamine receptor stimulation at the level of the kidney.

Several hemodynamic variables differed significantly between the two groups in a manner consistent with the hyperdynamic response to injury. The patients as a group had significantly greater GFR, RPF, and CI than did the controls, which is in agreement with previous studies.[7,10] Despite the presence of a hyperdynamic circulation, patients also had a negative free water clearance and significantly lower fractional excretions of sodium than controls, values consistent with the paradoxical blood volume deficit we have previously reported to be present in burn patients during the post-resuscitative phase.[7] This difference was further characterized by a lack of significant correlation between ERPF and urine flow in the patients that was present in the controls ($r = 0.788$; $p < 0.05$). The control subjects reacted to low-dose dopamine in a manner consistent with published reports.[2-5] Effective renal plasma flow, urine flow, and sodium excretion were significantly increased, findings previously reported to be the result of dopamine-1 receptor stimulation. Renal plasma flow increased in both groups, and remained elevated for the entire 3-hour dopamine infusion. The mechanism responsible for this increase appears to involve alterations in cardiac function and the renal vascular bed. Cardiac output was significantly increased in all patients during dopamine infusion. Dopamine (3 μg/kg/min) had a significant chronotropic effect, contributing to the increase in cardiac output. Stroke volume was not increased, suggesting a negligible effect of the decrease in afterload and the lack of a pure inotropic effect of the dopamine.

The significant chronotropic response at this low infusion rate of dopamine suggests an increased sensitivity of cardiac beta-adrenergic receptors in spite of the elevated beta-adrenergic activity previously documented in thermally injured patients. Other studies have failed to document a chronotropic effect of this dose of dopamine, rather, they have demonstrated an increase in cardiac output primarily mediated by a reduction in left ventricular afterload.[11,12] Despite the decrease in systemic vascular resistance, the chronotropic effect may impose increased work on the already hyperdynamic myocardium. A similar hemodynamic profile with a chronotropic effect has been documented during infusion of higher doses of dopamine, which have resulted in an increased

systemic oxygen consumption measured by computerized indirect calorimetry.[12]

To determine if the increase in effective renal plasma flow of the patients was mediated by changes in cardiac output, we compared the percentage of cardiac output represented by renal plasma flow before and during dopamine therapy. While patients were on dopamine, this mean value increased from 5.24% to 5.98% ($p = 0.01$). However, as depicted in Figure 6, this ratio did not change in five of the ten patients, indicating that the augmented cardiac output contributed to the increase in effective renal plasma flow in the majority of these patients.

It was not possible to predict the changes in ERPF or GFR from the urine flow or natriuretic response to dopamine in either the patients or the controls; a similar finding was reported by Smit et al. in normal humans.[13] Thus the absence of a diuresis does not preclude an increase in GFR or ERPF in this sample of thermally injured patients. Baseline ERPF did not correlate with Δ ERPF in our controls or patients. This is in contrast to previously published data from Schwartz[14] and Beukhof,[15] who studied patients undergoing vascular surgery and those with glomerulopathy, respectively. Both of these patient groups consisted of a large number of individuals with low baseline ERPF and significant renal dysfunction, making them distinctly different from our patients and possibly explaining this discrepancy.

The natriuretic effect of low-dose dopamine in the patients was quite variable. There was a strong positive correlation between pre-dopamine sodium excretion and the increase in sodium excretion while patients were receiving dopamine ($r = 0.758$; $p = 0.011$). The patients with pre-dopamine sodium excretions less than 5 mEq/h/1.73 m^2 did not demonstrate appreciably increased sodium excretion with dopamine therapy. These patients may have had a relative intravascular volume deficit, whereby other control mechanisms may obscure a direct inhibitory effect of dopamine on proximal tubule sodium transport.[7,16]

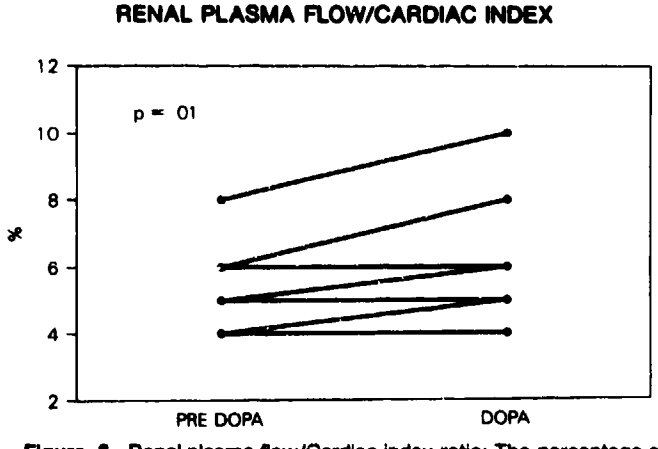

Figure 6. Renal plasma flow/Cardiac index ratio: The percentage of cardiac output comprising renal plasma flow before and during dopamine is depicted for each patient (n = 9). Although the difference was significant ($p = 0.01$), five patients demonstrated no increase in this ratio, suggesting that the increase in renal plasma flow contributed to the increase in cardiac output. The two lowest horizontal lines each represent data from two patients.

We did not document a significant effect of low-dose dopamine on osmolar clearance in this patient population. Parker and associates documented a significant increase in osmolar clearance in conjunction with increased GFR in a group of critically ill oliguric patients.[17] Presumably, the lack of a significant increase in the already elevated GFR prevented this desirable effect in our group of hypermetabolic burn patients.

Low-dose dopamine has been reported to affect deleteriously the distribution of microcirculatory blood flow in the liver and skeletal muscle of normal rats despite a reduction in systemic vascular resistance.[18] Lundberg reported a failure of low-dose dopamine to increase mesenteric blood flow despite a drop in systemic vascular resistance in the setting of elevated sympathetic nervous system activity,[19] a milieu known to exist in burn patients.[10] The redistribution of flow suggests the possibility of either a steal phenomenon in which DA-1 receptor-mediated vasodilatation in some beds results in decreased flow to those vascular beds without these receptors or altered alpha receptor sensitivity to low dose dopamine. Although altered alpha receptor sensitivity has not been documented in normal humans receiving low-dose dopamine, it has been documented to occur in preterm neonates.[20] Whether such alpha receptor changes were present in our patients is unknown. Our finding of altered beta receptor sensitivity with the associated potential for maldistribution of blood flow and increased oxygen consumption suggests that low-dose dopamine therapy may not be innocuous in thermally injured patients. Further studies delineating the effect of this therapy on distribution of cardiac output and alterations in the oxygen availability ratio are necessary to document its safety. Finally, the benefit of maintaining an effective renal plasma flow at levels higher than those normally present in the thermally injured patient remains to be proven.

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DISCUSSION

Dr. Robert C. Mackersie (San Francisco, California): The central issue toward which this study is directed is the ultimate clinical utility of low-dose dopamine, either in indicated treatment or for prophylaxis. The question is going to be answered by determining the salutary effects versus the side effects in presumably a selected population of massive burn patients.

This is one in a series of studies from the U.S. Army Institute of Surgical Research that provides some new data on renal and hemodynamic effects of low-dose dopamine in burn patients and expands our understanding, I think, of this treatment regimen. It does so as a descriptive, nonrandomized, but comparative study of patients with major burns and normal subjects.

The study utilizes a relatively small number of patients who sustained major burns. There was a reasonably narrow age distribution, and the experimental measurements were carefully conducted.

I would regard this, however, as a preliminary study, and although stimulating, it does not allow us to draw conclusions regarding the overall clinical utility of low-dose dopamine, the side effects of low-dose dopamine in burn patients, or the mechanisms responsible for the observed physiologic changes.

I think the major limiting factor was a fairly striking lack of consistent physiologic responses to the low-dose dopamine in this group. This is particularly true of urine output as pointed out, sodium excretion, and the renal plasma flow/cardiac index ratio. It appears as though these groups exhibited a bimodal distribution, with the sodium excretion being the most striking.

The questions I have pertain mostly to the potential reasons for these inconsistent clinical responses to low-dose dopamine. One, could you please comment on the choice of the study period? These patients averaged 19.5 days postburn and ranged from 9 to 32 days. Lots of things change in the first 2 weeks postburn, and the potential for low-dose dopamine's clinical utility is likely earlier than 2½ to 3 weeks. An earlier study period perhaps would be more appropriate.

Two, how much disparity was there in burn wound coverage, or burn wound management during the time of this study? There was a noted absence of sepsis or evidence of infection, but might differences in burn wounds contribute to the variable responses observed?

Three, the sodium intake before the study was not standardized in your patients, being "tailored according to patients' fluid and electrolyte status," with some patients receiving enteral nutrition as well. Did you examine sodium intake and any possible effects on the renal response to low-dose dopamine in these patients?

Four, the group down at Fort Sam Houston has previously described a disassociation, as was pointed out, between directly measured blood volume and potential indices of blood volume flow. To what extent do you think this may have contributed to the inconsistent responses to low-dose dopamine in this study?

Five, other than tachycardia, which may be a good index of sympathetic drive, there were no data examining the catecholamine or hormonal (e.g., angiotensin AVP, atrial natriuretic factor) environment of these patients. Do you think some of the potential variability in these elements contributed to the differences in response you observed?

Six, how did you decide on 3 μg/kg/min per dosing, with most of the other studies running around 0.5–2 μg/kg/min? Aren't you potentially muddying the water a little bit by sneaking up on the beta activation range for dopamine?

Seven, in your conclusion, you provided a warning regarding side effects of blood flow redistribution in the organ beds and increased cardiac work with low-dose dopamine, neither of which was documented by the data here. Do you have any reason to think these are real as opposed to theoretical adverse effects in patients with major burns?

Determining the ultimate benefit of low dose dopamine in burn patients will depend on defining a target population (one susceptible to the salutary effects), documenting both clinical and physiologic outcome, and careful observation for adverse side effects.

I think this study provides a good start. I enjoyed the paper very much.

Dr. Charles E. Lucas (Detroit, Michigan): This very important paper, in my opinion, challenges the concept that, in humans, there is a dopaminergic receptor in the kidney that allows for selective renovasal dilation independent of changes in cardiac output. This concept dates back 20 years to a paper that used historical controls and inadequate, indirect measurements or estimates of renal plasma flow, and atrocious statistical methods. I cannot remember the authors of that paper, but I hope none of them are here today.

Despite the fact that we learned in our first year of medical school that urine output is independent of both renal blood flow and glomerular filtration rate within wide ranges of normal, it has become the standard throughout the land to say, in an intensive care unit, "We started this patient on dopamine, low dose. The patient had a good response in urine output, and therefore the patient had this dopaminergic response with increase in renal blood flow." What nonsense!

The authors today have demonstrated that the changes in renal dynamics are related more to the changes in the heart and not to some mythical change in the kidney related to this mythical receptor.

I would suggest that had they measured the cardiac output in their control patients, they would have demonstrated the same increase in cardiac output as the cause for their changes in the study patients.

We have demonstrated identical findings in both injured and septic patients and are in complete and total agreement with the authors. The fact that they demonstrated the increased cardiac output suggests very strongly that the increase in urine output is as we learned in that first year of medical school; namely, changes in antidiuretic hormone release as the subtle increases in cardiac stimulate output baroreceptors that shut off the release of antidiuretic hormone.

My only question is have the authors measured systemic and urinary cyclic AMPs, a second messenger in ADH activity, to see if there is a suggestion for decreased ADH release. Incidentally, if the urine and serum are stored in a very cold freezer, these can be measured long after collection.

Dr. Theresa A. Graves (Closing): Thank you, Dr. Mackersie, for reviewing our manuscript. The central thrust of this preliminary study was to determine if low-dose dopamine had any efficacy in a select group of hypermetabolic, post-resuscitative burn patients. Toward this end we verified our techniques in a normal control group to demonstrate the reproducibility of the expected physiologic renal response to low-dose dopamine. In addition, patients served as their own controls before dopamine infusion, thus allowing paired comparisons.

We chose 3 μg/kg/min of dopamine because that value is within the mid-range of published infusion rates for which one should expect dopaminergic responses. With this infusion rate we documented in the normal controls a physiologic response consistent with published reports. The patients were heterogeneous in their response in that, in spite of a uniform increase in urine output and Cardiac Index, a consistent increase in renal plasma flow and natriuresis could not be demonstrated in all patients.

Most of your questions center around study design factors that may have contributed to the variable responses in the patients. We studied the patients on an average of 19.5 days following injury, a point in time when the patients are in the post-resuscitative flow phase of injury. We have previously documented, and again in this study have documented, a consistent, uniform hyperdynamic response to be present at this time following injury. Univariate analysis of initial burn size and dopamine response failed to demonstrate a significant correlation between these two variables. The degree of burn wound coverage following surgery was not isolated as a variable. Before the study, sodium intake was not standardized, and was varied according to patient requirements based upon measurements of serum electrolytes and urine output. All patients were receiving enteral nutritional support via a small intestinal feeding tube to meet their measured requirements.

We feel that the variability of responses to low-dose dopamine in our patients may well be a reflection of a blood volume deficit we have previously documented to be present in this type of post-resuscitative patient in spite of their hyperdynamic circulation. In our previous studies, patients with the most profound blood volume deficits had significantly elevated plasma levels of vasopressin, aldosterone, and plasma renin activity. The predominant effect of these hormones would be to inhibit dopamine-mediated natriuresis and diuresis. Because the hormonal response to a blood volume deficit depends upon the magnitude of this deficit, it is not surprising that the renal response to dopamine would also vary dependent upon this deficit.

This study was not designed to investigate whether dopamine infusion redistributed blood flow to specific organ beds or increased cardiac work. However, animal studies have documented detrimental malperfusion of the small bowel during low-dose dopamine infusion, especially in the setting of an elevated catecholamine response, the latter a condition similar to that of our patients. Dr. Rudeman's work in normal humans in which he varied dopamine infusion rates from 2.5 to 10 μg/kg/min demonstrated an increase in oxygen consumption that correlated with the onset of the chronotropic response. The measurement of cardiac work and oxygen consumption should be obtained in further evaluations of low-dose dopamine. We also feel that an evaluation of the microcirculatory effects of low-dose dopamine should be undertaken to dissect whether dopamine-mediated increases in renal blood flow result in a steal phenomena causing a relative decrease in perfusion in the splanchnic and hepatic circulation.

Dr. Lucas, thank you for your kind comments. We completely agree with your suggestion that if we had measured cardiac output in the controls it would likely have been elevated similar to that documented in the patients. We did not measure urinary or systemic cyclic AMP, but have stored urine and blood samples that could be assayed. Thank you for this insightful suggestion.

PLEASE NOTE CORRECTION FOR TYPOGRAPHICAL ERROR:

The standard deviation for glomerular filtration rate for controls before Dopamine infusion is listed as +/- 45 in Table 4, and +/- 4.5 in Table 5; the correct standard deviation is +/- 4.5.